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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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FROMMER LAWRENCE & HAUG
745 FIFTH AVENUE- 10TH FL.
NEW YORK, NY 10151

EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	PAPER NUMBER
1632	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/052,323	TANG ET AL.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-17,20-26,28-32,35-40 and 45* is/are pending in the application.

4a) Of the above claim(s) *3,7 and 8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6,9-17,20-26,28-32,35-40 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/30/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The examiner prosecuting this case has changed. All inquiries directed to the application should be directed to examiner W. - C. Winston Shen.

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06/16/2009 has been entered.

Claims 1 and 45 are amended. Claims 1, 3, 4, 6-17, 20-26, 28-32, 35-40, and 45 are pending in the present application.

Applicants previously elected *Escherichia* as a species of the bacterial vector. Therefore, claims 3, 7, and 8 were withdrawn previously because they are directed to non-elected species.

Accordingly, claims 1, 4, 6, 9-17, 20-26, 28-32, 35-40, and 45 are examined on the merits herein with the aforementioned elected species.

Priority

The present application is a continuation-in-part of U.S. Serial No. 09/563,826, filed 5/31/00, now US Patent 6,348,450; which claims benefit to 60/132,216, filed on 5/3/1999; and is a continuation-in-part of U.S. Serial No. 09/533,149, filed 3/23/00, now US Patent 6,716,823; which is a continuation-in-part of U.S. Serial No. 09/402,527, filed 01/03/2000, now US Patent 6,706,693; which is a 371 national stage entry of PCT/US98/16739, filed on 8/13/1998; which

claims benefit to provisional applications 60/055,520, filed on 8/13/1997 and 60/075,113, filed on 2/11/1998.

Upon review of the specifications of the above non-provisional U.S. applications and the above provisional applications and comparison with the specification of the present application, it is determined that the priority of amended 1, 3, 4, 6-17, 20-26, 28-32, 35-40, and 45 is 01/18/2002, the filing date of instant application. The determination is based on that the limitation "live bacterial vector" recited in amended independent claim 1 as well as the limitation "live gram-negative bacterial vector" recited in amended independent claim 45 is first disclosed in the instant application.

Claim Objections

1. Claim 40 is objected to because of the following informalities: Claim 40 recites "The method of claim 6 or 43". However, claim 43 is cancelled. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. Previous rejection of claims 1, 9-14, 21-22, 25-26, 28-32, and 38 under 35 U.S.C. 102(e) as being anticipated by **Roop et al.** (US 6,143,727 with the effective filing date of at least 11/1/1993), is ***withdrawn*** because the claims have been amended.

Amended claim 1 filed on 05/18/2009 reads as follows: A method of non-invasive immunization in an animal and/or a method of inducing a systemic immune response or systemic therapeutic response to a gene product, in an animal, comprising removing the cornified epithelium from the skin of the animal and contacting the outer most layer of the exposed skin of the animal with a live bacterial vector that contains and expresses a nucleic acid molecule encoding the gene product, in an amount effective to induce the response.

Roop et al. does not teach the amended limitation "removing the cornified epithelium from the skin of the animal and contacting the outer most layer of the exposed skin of the animal with a live bacterial vector" recited in claim 1. Claims 9-14, 21-22, 25-26, 28-32, and 38 depend from claim 1.

3. Previous rejection of claims 1, 9-14, 21-22, 25-26, 28-32, and 38 under 35 U.S.C. 102(e) as being anticipated by **Carson et al.** (US 5,679,647 with the effective filing date of at least 11/3/1994; IDS) for essentially same reasons already set forth in the Office action mailed on 3/19/08 (pages 6-7), is ***withdrawn*** because the claims have been amended.

Amended claim 1 filed on 05/18/2009 reads as follows: A method of non-invasive immunization in an animal and/or a method of inducing a systemic immune response or systemic therapeutic response to a gene product, in an animal, comprising removing the cornified epithelium from the skin of the animal and contacting the outer most layer of the exposed skin of

the animal with a live bacterial vector that contains and expresses a nucleic acid molecule encoding the gene product, in an amount effective to induce the response.

Carson et al. does not teach the amended limitation "removing the cornified epithelium from the skin of the animal and contacting the outer most layer of the exposed skin of the animal with a live bacterial vector" recited in claim 1. Claims 9-14, 21-22, 25-26, 28-32, and 38 depend from claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Previous rejection of claims 1, 4, 6, 15-17, 20, 23-24, 35-37, and 40 under 35 U.S.C. 103(a) as being unpatentable over either **Powell et al.** (US 5,877,159) or **WO 01/89535 A1** in view of **Roop et al.** (US 6,143,727 with the effective filing date of at least 11/1/1993) for the same reasons already set forth in the Office action mailed on 03/19/08 (pages 8-11), is ***withdrawn*** because the claims have been amended.

Amended claim 1 filed on 05/18/2009 reads as follows: A method of non-invasive immunization in an animal and/or a method of inducing a systemic immune response or systemic therapeutic response to a gene product, in an animal, comprising removing the cornified epithelium from the skin of the animal and contacting the outer most layer of the exposed skin of

the animal with a live bacterial vector that contains and expresses a nucleic acid molecule encoding the gene product, in an amount effective to induce the response.

None of Powell et al (US 5,877,159), WO 01/89535, and Roop et al. teaches the amended limitation "removing the cornified epithelium from the skin of the animal and contacting the outer most layer of the exposed skin of the animal with a live bacterial vector" recited in claim 1. Claims 4, 6, 15-17, 20, 23-24, 35-37, and 40 depend from claim 1.

5. Previous rejection of claims 1, 29 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over either **Carson et al.** (US 5,679,647 with the effective filing date of at least 11/3/1994; IDS) or **Roop et al.** (US 6,143,727 with the effective filing date of at least 11/1/1993) in view of either **Alexander et al.** (Human Mol. Genetics 4:2279-2285, 1995; IDS) or **Li et al.** (Nature Med. 1:705-706, 1995; IDS), is ***withdrawn*** because the claims have been amended.

Amended claim 1 filed on 05/18/2009 reads as follows: A method of non-invasive immunization in an animal and/or a method of inducing a systemic immune response or systemic therapeutic response to a gene product, in an animal, comprising removing the cornified epithelium from the skin of the animal and contacting the outer most layer of the exposed skin of the animal with a live bacterial vector that contains and expresses a nucleic acid molecule encoding the gene product, in an amount effective to induce the response.

None of Carson et al., Roop et al., Alexander et al. and Li et al. teaches the amended limitation "removing the cornified epithelium from the skin of the animal and contacting the outer most layer of the exposed skin of the animal with a live bacterial vector" recited in claim 1. Claims 29 and 39 depend from claim 1.

6. Previous rejection of claim 45 under 35 U.S.C. 103(a) as being unpatentable over either **Powell et al.** (US 5,877,159) or **WO 01/89535 A1** in view of **Roop et al.** (US 6,143,727 with the effective filing date of at least 11/1/1993) as applied to claims 1, 9-14, 21-22, 25-26, 28-32, 38 and 43 above, and further in view of **Robinson et al.** (US 6,841,381), is ***withdrawn*** because the claims have been amended.

Amended claim 45 filed on 05/18/2009 reads as follows: A method of non-invasive immunization in an animal and/or a method of inducing a systemic immune response or systemic therapeutic response to a gene product, in an animal, comprising removing the cornified epithelium from the skin and topically administering to the outer most layer of the exposed skin of the animal a live gram-negative bacterial vector that contains and expresses a nucleic acid molecule encoding the gene product, in an amount effective to induce the response.

None of Powell et al (US 5,877,159), WO 01/89535 A1, Roop et al., and Robinson et al. (US 6,841,381) teaches the amended limitation "administering to the outer most layer of the exposed skin of the animal a live gram-negative bacterial vector" recited in claim 45.

The following 103 rejection is necessitated by claim amendments filed on 05/18/2009.

7. Claims 1, 4, 6, 9-17, 20-26, 28-32, 35-40, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Powell et al.** (US patent 5,877,159, issued on 03/02/1999, filed on 05/03/1995) in view of **Robinson et al.** (US patent 6,841,381, issued on 01/11/2005, filed on

01/27/1994), **Glenn et al.** (WO 98/20734, publication date 05/22/1998, filing date 11/14/1997), and **Carson et al.** (US patent 5,679,647, issued on 10/21/1997, filed on 11/03/1994).

Amended claim 1 filed on 05/18/2009 reads as follows: A method of non-invasive immunization in an animal and/or a method of inducing a systemic immune response or systemic therapeutic response to a gene product, in an animal, comprising removing the cornified epithelium from the skin of the animal and contacting the outer most layer of the exposed skin of the animal with a live bacterial vector that contains and expresses a nucleic acid molecule encoding the gene product, in an amount effective to induce the response.

Amended claim 45 filed on 05/18/2009 reads as follows: A method of non-invasive immunization in an animal and/or a method of inducing a systemic immune response or systemic therapeutic response to a gene product, in an animal, comprising removing the cornified epithelium from the skin and topically administering to the outer most layer of the exposed skin of the animal a live gram-negative bacterial vector that contains and expresses a nucleic acid molecule encoding the gene product, in an amount effective to induce the response.

Claim interpretation: The limitation "a live bacteria vector" recited in claim 1 is interpreted as any bacteria that can express endogenous and exogenous nucleic acid in the bacteria. Similarly, and "a live gram-negative bacterial vector" recited in claim 45 is interpreted as any Gram-negative bacteria that can express endogenous and exogenous nucleic acid in the bacteria. Accordingly, a live bacterial vector encompasses any attenuated bacteria by any means, and "a live gram-negative bacterial vector" encompasses any attenuated Gram-negative bacteria by any means.

With regard to the limitation of claims 1, 4, 6, 9-12, 14, 15, 20, 25, 26, 28-32, 38-40, and 45, Powell et al. teaches a method for introducing and expressing genes in animal cells comprising infecting said animal cells with live and attenuated invasive bacteria, wherein said bacteria contain a eukaryotic expression cassette encoding said gene. The gene may encode, e.g., a vaccine antigen, a therapeutic agent, an immunoregulatory agent (See abstract, Powell et al., 1999). Powell et al. teaches that the invasive bacteria containing the eukaryotic expression cassettes can be introduced to infect the animal by intravenous, intramuscular, *intradermal*, intraperitoneally, peroral, intranasal, intraocular, intrarectal, intravaginal, oral, immersion and intraurethral inoculation routes (See lines 50-55, column 19, Powell et al., 1999). Powell et al. teaches the development of an immune response to an *in vivo* delivered gene via bactofection by administering 5 x10^7 *S. flexneri* (*Shigella flexneri,* which is a Gram-negative bacterium) *Δaro ΔvirG* strain (which rendered the bacterium attenuated, and is encompassed by limitation "a live bacterial vector" recited in claim 1 and "a live gram-negative bacterial vector" recited in claim 45 of instant application) containing the pCEP4::gp160 plasmid construct (which is encompassed by "a nucleic acid molecule encoding the gene product" that induces "systemic immune response" recited in claim 1 and 45) *intranasally* to restrained Balb/c mice, and 14 days following bactofection, the mice were sacrificed and spleens collected. Splenocytes isolated from mice bactofected with plasmid pCEP4::gp160, containing the gene for HIV-1 gp160, showed a seven-fold stimulation, while splenocytes from control (pCEP4) bactofected mice showed no response (See Example 7, bridging paragraph columns 25-26, Powell et al., 1999). Powell et al. reaches that attenuated bacteria can be *Escherichia coli* (which reads on the

limitations recited in claims 4, 6, and 45 of instant application) (See lines 43-47 of column 8, and line 48 of column 10, Powell et al., 1999).

With regard to the limitation pertaining to induction of a systemic immunological response pertaining to nucleic acid encoding a therapeutic product (which reads on a growth factor) recited in claim 13, and immunomodulator (which reads on a cytokine) recited in claim 17, Powell et al. teaches that live invasive bacteria can deliver eukaryotic expression cassettes encoding immuno-regulatory molecules. These immuno-regulatory molecules include, but are not limited to, growth factors, such as M-CSF, GM-CSF; and cytokines, such as IL-2, IL-4, IL-5, IL-6, IL-10, IL-12 or IFNγ, and delivery of cytokines expression cassettes to tumor tissue has been shown to stimulate potent systemic immunity and enhanced tumor antigen presentation without producing a systemic cytokine toxicity (see lines 32-40, column 18, Powell et al., 1999).

With regard to response against *Clostridium tetani* infection and nucleic acid encodes tetanus toxin recited in claims 16 and 35-37, Powell et al. teaches examples of protective antigens of bacterial pathogens include the *Shigella sonnei* form 1 antigen; the O-antigen of *V. cholerae* Inaba strain 569B; protective antigens of enterotoxigenic *E. coli*, such as the CFA/I fimbrial antigen and the nontoxic B-subunit of the heat-labile toxin; pertactin of *Bordetella pertussis*, adenylate cyclase-hemolysin of *B. pertussis*, and fragment C of tetanus toxin of *Clostridium tetani* (See lines 29-42, column 17, Powell et al., 1999).

With regard to the limitation of various animals recited in claims 21-24, Powell et al. teaches that preferred animal cells are mammalian cells, such as humans, bovine, ovine, porcine, feline, buffalo, canine, goat, equine, donkey, deer, and primate cells, and the most preferred animal cells are human cells (See lines 1-4, column 8, Powell et al., 1999).

Powell et al. does not explicitly teach **(i)** the limitation "removing the cornified epithelium from the skin of the animal and contacting the outer most layer of the exposed skin of the animal" recited in claim 1, and similar limitation "removing the cornified epithelium from the skin and topically administering to the outer most layer of the exposed skin of the animal" recited in claim 45, and **(ii)** the limitations pertaining to delivery device to the skin of the animal recited in claims 29-32, 38 and 39.

(i) With regard to the limitation "removing the cornified epithelium from the skin of the animal and contacting the outer most layer of the exposed skin of the animal" and the limitation "removing the cornified epithelium from the skin and topically administering to the outer most layer of the exposed skin of the animal" recited in claims 1 and 45 respectively, **Robinson et al.** teaches a method of immunizing a vertebrate, comprising introducing into the vertebrate a DNA transcription unit which comprises DNA encoding a desired antigen or antigens. The uptake of the DNA transcription unit by a host vertebrate results in the expression of the desired antigen or antigens, thereby eliciting humoral or cell-mediated immune responses or both humoral and cell-mediated responses. The elicited humoral and cell-mediated immune response can provide protection against infection by pathogenic agents, provide an anti-tumor response, or provide contraception. The host can be any vertebrate, avian or mammal, including humans (See abstract, Robinson et al., 2005). Robinson et al. teaches that animals were anesthetized with 30 μl of Ketaset/Rompun (10:2); abdominal target areas were shaved and treated with Nair (Carter-Wallace, New York; which reads on limitation of claim 39 of instant application) for two

minutes to *remove residual stubble and stratum corneum* (which is encompassed by the limitation "removing the cornified epithelium" recited in claims 1 and 45 of instant application), and target areas were thoroughly rinsed with water prior to gene delivery. DNA-coated gold particles were delivered into abdominal skin with the Accell instrument, which employs an electric spark discharge as the motive force (Yang, M. S. et al., *Proc. Natl. Acad. Sci. USA* 87: 9568-9572 (1990)) (See lines 25-35, column 15, Robinson, 2005). Additionally, **Glenn et al. et al.** teaches transcutaneous immunization system delivering antigen to immune cells without perforation of the skin (See abstract, Glenn et al.), the antigen may pass through the normal protective outer layers of the skin (i.e. *stratum cornum*, the outermost layer of the skin consisting of *cornified cells* and lipid) and induce the immune response directly through an antigen presenting cells (e.g. macrophage, tissue macrophage, Langerhans cell, dendritic cell, dermal dendritic cell, B lymphocyte, or Kuffer cell) that presents processed antigens to a T lymphocyte (See bridging paragraph of page 10-11, and lines 24-35 of page 12, Glenn et al.). Glenn et al teaches immunization procedure either with or without shaving skin of mouse prior to delivery of immunogen (which reads on the limitations of claims 38 and 39 of instant application). Glenn et al. et al. further teaches antigens from bacteria including anthrax, enterorotoxigenic *E. coli*, C. tetanus (See lines 17-25 of page 17, Glenn et al.), and antigens from *C. botulinum* toxin C2, and C. *botulinum* toxin C3 (See lines 13-23 of page 19, Glenn et al.).

Furthermore, **Carson et al.** teaches means for, and routes of, administration of naked polynucleotides: For dermal routes of administration, the means of introduction may be by epidermal administration, subcutaneous or intradermal injection (which reads on epidermal cells recited in claim 17 of instant application). Of these means, epidermal administration is preferred

for the greater concentrations of APC's (Antigen Presenting Cells) expected to be in intradermal tissue. The means of introduction for dermal routes of administration which are most preferred, however, are those which are *least invasive*. Preferred among these means *are transdermal transmission* and *epidermal administration*. For transdermal transmission, iontophoresis is a suitable method. Iontophoretic transmission may be accomplished using commercially available "patches" which deliver their product continuously through unbroken skin (which reads on non-invasive immunization recite din claims 1 and 45 of instant application) for periods of several days or more (See lines 2-18, column 19, and lines 26-38, column 9, Carson et al., 1997). Carson et al. teaches that epidermal administration essentially involves mechanically or chemically irritating the outermost layer of the epidermis sufficiently to provoke an immune response to the irritant. Specifically, the irritation should be sufficient to attract APC's to the site of irritation, and it is believed that the APC's (Antigen Presenting Cells) then take up and express the administered naked polynucleotide (which reads on the limitation "the hair is not removed from the skin recited in claim 38 of instant application) (See lines 33-39, column 19, Carson et al., 1997). Carson et al. teaches that another suitable approach to epidermal administration of naked polynucleotides is by use of a chemical which irritates the outermost cells of the epidermis, thus provoking a sufficient immune response to attract APC's (Antigen Presenting Cells) to the area. An example is a keratinolytic agent, such as the salicylic acid used in the commercially available topical depilatory cream sold by Noxema Corporation under the trademark NAIR (which reads on the limitation "the hair is removed from the skin recited in claim 39 of instant application) (See bridging paragraph, paragraphs 19-20, Carson et al., 1997).

(ii) With regard to the limitations pertaining to delivery device to the skin of the animal recited in claims 29-32, **Robinson et al.** teaches protective immunizations by gene gun delivery of DNA to the mouse epidermis using the Accell particle bombardment device (Agracetus, Middleton, Wis.) (See Example 6, columns 14-15, Robinson et al., 2005). Furthermore, **Carson et al.** teaches an exemplary mechanical irritant means employs a multiplicity of very narrow diameter, short tynes which can be used to irritate the skin and attract APC's (Antigen Presenting Cells) to the site of irritation, to take up naked polynucleotides transferred from the end of the tynes. For example, the MONO-VACC old tuberculin test manufactured by Pastuer Merieux of Lyon, France contains a device suitable for introduction of naked polynucleotides. The device (which is distributed in the U.S. by Connaught Laboratories, Inc. of Swiftwater, Pa.) consists of a plastic container having a syringe plunger at one end and a tyne disk at the other. The tyne disk supports a multiplicity of narrow diameter tynes of a length which will just scratch the outermost layer of epidermal cells (which reads on non-invasive immunization recite din claims 1 and 45 of instant application). Each of the tynes in the MONO-VACC kit is coated with old tuberculin; in the present invention, each needle is coated with a pharmaceutical composition of naked polynucleotide or a mixture thereof. Use of the device is according to the manufacturer's written instructions included with the device product; these instructions regarding use and administration are incorporated herein by this reference to illustrate conventional use of the device. Similar devices which may also be used in this embodiment are those which are currently used to perform allergy tests, in the context of non-invasive immunization (See 40-53 of column 19, and lines 24-34 of column 1, Carson et al., 1997).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the teachings of Powell et al. regarding a method for introducing and expressing genes in animal cells comprising infecting said animal cells with live and attenuated invasive bacteria, wherein said bacteria contain a eukaryotic expression cassette encoding said gene, and the gene may encode, e.g., a vaccine antigen, an immuno-regulatory agent, with the teachings of Robinson et al. and Glenn et al. regarding to removal of residual stubble and stratum corneum (outer layer of skin) layer of epidermis for delivery of DNA of interest, the teachings of Glenn et al. regarding various antigens expressed by nucleic acid molecules, and the teachings of Carson et al. regarding preferred routes of administration for inducing local immunity in or near the skin by transdermal transmission, intradermal injection or superficially scratching or irritating the outermost layer of epidermal cells, to arrive at the claimed methods recited in claims 1, 4, 6, 9-17, 20-26, 28-32, 35-40, and 45.

One having ordinary skill in the art would have been motivated to combine the teachings of Powell et al., Robinson et al., Glenn et al, and Carson et al. because Powell et al. teaches multiple routes for administration, including intranaral and intradermal administration, of a bacterial cell as a vector to induce systemic immune response; Robinson et al. and Glenn et al. teach the removal of residual stubble and cornified stratum corneum layer of skin for topical administration; Powell et al. and Glenn et al. teach various antigens expressed by nucleic acid molecules for immunization, and Carson et al. teaches the benefits of transdermal transmission and epidermal administration being non-invasive and being effective in delivery of DNA that leads to induction of an immune response.

There would have been a reasonable expectation of success given (i) successful demonstration of the development of an immune response to an *in vivo* delivered gene via bactofection by administering 5 x10^7 *S. flexneri* (*Shigella flexneri*) *Δaro ΔvirG* strain containing the pCEP4::gp160 plasmid construct intranasally to restrained Balb/c mice, and 14 days following bactofection, by the teachings of Powell et al.; (ii) successful demonstration of the removal of residual stubble and cornified stratum corneum layer of skin for epidermal administration for DNA that induces immune response against H1N1 influenza, by the teachings Robinson et al. (See Example 6, columns 15-16, Table 8) and Glenn et al. (See bridging paragraph of page 10-11, and lines 24-35 of page 12, Glenn et al.); and (iii) successful demonstration of selective induction of cytotoxic T lymphocyte response after intradermal administration of naked polynucleotides encoding ovalbumin, by the teachings of Carson et al. (See Example IX, columns 34-35).

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Applicant's arguments and Response to Applicant's arguments

Applicant's remarks regarding the previous rejection of record are addressed as the related to the new grounds of rejection set forth above.

Applicant argues that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings (See page 9 of Applicant's remarks filed on 05/18/2009).

In response, the Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a

specific teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf). The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.,* the suggestion and motivation to combine Powell et al., Robinson et al., Glenn et al, and Carson et al. has been clearly set forth above in this office action.

Applicant argues that none of the cited references under the § 103 rejection indicate that there would be an expectation of success if one were to apply live bacterial vectors to the outmost layer of de-cornified skin. Applicants argues that the fact that neither Powell et al. nor WO 01/89535 teach topical application suggests that there was not an expectation that such a non-invasive method for application of live cells to an animal would prove effective (See page 10 of Applicant's remarks filed on 05/18/2009).

In response, the Examiner notes that previous 103 rejections documented in the Final office action mailed on 12/16/2008 have been withdrawn. The amended limitation pertaining to a non-invasive method comprising "removing the cornified epithelium from the skin of the animal and contacting the outer most layer of the exposed skin of the animal with a live bacterial vector" have been fully considered and addressed in the new grounds of rejection of claims 1, 4, 6, 9-17, 20-26, 28-32, 35-40, and 45 under 35 U.S.C. 103(a) as being unpatentable over Powell et al. (US patent 5,877,159, issued on 03/02/1999, filed on 05/03/1995) in view of Robinson et al. (US patent 6,841,381, issued on 01/11/2005, file don 01/27/1994), Glenn et al. (WO

98/20734, publication date 05/22/1998, filing date 11/14/1997), and Carson et al. (US patent 5,679,647, issued on 10/21/1997, filed on 11/03/1994).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Previous rejection of claims 1, 9-14, 21-22, 25-26, 28-31, 38-39 and 43 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,706,693 for the same reasons already set forth in the Office action mailed on 3/19/08 (pages 16-17), is ***withdrawn*** because the claims have been amended.

The claims of instant application have been amended to administration of live bacterial vector whereas claims 1-3 of U.S. Patent No. 6,706,693 are directed to administration of plasmid DNA vector.

9. Previous rejection of claims 1, 11-13, 25-26, 28-32, 38-39 and 43 are provisionally rejected under **35 U.S.C. 101** as claiming the same invention as that of claims 1, 6-8, 20-21, 23-27 and 33-35 of copending Application No. 10/116,963, is ***withdrawn*** because the claims have been amended.

The claims of instant application have been amended to administration of live bacterial vector whereas claims 1, 6-8, 20-21, 23-27 and 33-35 of copending Application No. 10/116,963 are directed to administration of bacterial vector, which is broader in scope than the scope of claims of instant application.

10. Claims 1, 4, 6, 9-17, 20-26, 28-32, 35-40, and 45 of instant application 10/052,323 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1, 4, 6-8, 12, 16-29, and 33-36 of the co-pending application No. **10/116,963**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the independent claim 1 of instant application 10/052,323 filed on 05/18/2009 is directed to a method of non-invasive immunization in an animal and/or a method of inducing a systemic immune response or systemic therapeutic response to a gene product, in an animal, comprising removing the cornified epithelium from the skin of the animal and contacting the outer most layer of the exposed skin of the animal with a live bacterial vector that

contains and expresses a nucleic acid molecule encoding the gene product, in an amount effective to induce the response. Independent claim 45 of instant U.S. application 10/052,323 filed on 05/18/2009 is directed to a method of non-invasive immunization in an animal and/or a method of inducing a systemic immune response or systemic therapeutic response to a gene product, in an animal, comprising removing the cornified epithelium from the skin and topically administering to the outer most layer of the exposed skin of the animal a live gram-negative bacterial vector that contains and expresses a nucleic acid molecule encoding the gene product, in an amount effective to induce the response. The independent claim 1 of co-pending application No. 10/116,963 filed on 06/05/2009 is directed to a method of non-invasive immunization in an animal and/or a method of inducing a systemic immune response to a gene product, in an animal, comprising ablating the skin of the animal and topically applying to the underlying skin of the animal a bacterial vector, wherein the vector comprises and expresses a nucleic acid molecule encoding the gene product, in an amount effective to induce the response. Independent claim 35 of co-pending application No. 10/116,963 filed on 06/05/2009 filed on 06/05/2009 is directed to a method of non-invasive immunization in an animal and/or a method of inducing a systemic immune response to a gene product, in an animal, comprising ablating the skin of the animal and topically applying to the underlying contacting skin of the animal a recombinant bacterial vector, wherein the vector comprises and expresses a nucleic acid molecule encoding the gene product, in an amount effective to induce the response.

It is noted the limitation "removing the cornified epithelium from the skin of the animal and contacting the outer most layer of the exposed skin of the animal with a live bacterial vector" recited in claim 1 of instant application 10/052,323 filed on 05/18/2009 is an obvious variant of

"ablating the skin of the animal and topically applying to the underlying skin of the animal a bacterial vector" recited in claim 1 of co-pending application 10/116,963, despite of slight difference between the scope of the claims of instant application 10/052,323 and the scope of claims of co-pending U.S. 10/116,963 application. It is further noted that the specification of co-pending application 11/116,963 states that "Preferably, the vector is a bacterial vector, wherein the bacteria are Escherichia. Preferably, the invention relates to such methods wherein the bacteria are *Escherichia coli*". (See paragraph [0011], claims 2 and 3, US 2003/0045, 492, publication of 10/116,963) and *E. coli* is encompassed by the limitation "bacterial vector' recited in claim 1 and encompassed by the limitation "gram-negative bacterial vector" recited in claim 45 of instant U.S. application 10/052,323.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 1, 4, 6, 9-17, 20-26, 28-32, 35-40, and 45 of instant application 10/052,323 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-30, 32-38, and 93 of the co-pending application No. **10/346, 021**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the independent claim 1 of instant application 10/052,323 filed on 05/18/2009 is directed to a method of non-invasive immunization in an animal and/or a method of inducing a systemic immune response or systemic therapeutic response to a gene product, in an animal, comprising removing the cornified epithelium from the skin of the animal and contacting the outer most layer of the exposed skin of the animal with a live bacterial vector that contains and expresses a

nucleic acid molecule encoding the gene product, in an amount effective to induce the response. Independent claim 45 of instant U.S. application 10/052,323 filed on 05/18/2009 is directed to a method of non-invasive immunization in an animal and/or a method of inducing a systemic immune response or systemic therapeutic response to a gene product, in an animal, comprising removing the cornified epithelium from the skin and topically administering to the outer most layer of the exposed skin of the animal a live gram-negative bacterial vector that contains and expresses a nucleic acid molecule encoding the gene product, in an amount effective to induce the response. The independent claim 1 of co-pending application No. 10/346,021 filed on 07/15/2009 is directed to a method of non-invasive immunization in an animal and/or a method of inducing a systemic immune response to a gene product, in an animal, comprising interrupting or ablating the stratum corneum layer of the epidermis and subsequently contacting skin of the animal with a non-replicative vector chosen from the group of bacterium and virus wherein the vector comprises and expresses a nucleic acid molecule encoding the gene product, in an amount effective to induce the response. Independent claim 93 of co-pending application No. 10/346,021 filed on 07/15/2009 is directed to a method of non-invasive immunization in an animal and/or a method of inducing a systemic immune response to a gene product, in an animal, comprising interrupting or ablating the stratum corneum layer of the epidermis and subsequently contacting skin of the animal with a non-replicative recombinant vector chosen from the group of bacterium and virus wherein the vector comprises and expresses a nucleic acid molecule encoding the gene product, in an amount effective to induce the response.

It is noted the limitation "removing the cornified epithelium from the skin of the animal and contacting the outer most layer of the exposed skin of the animal with a live bacterial vector" recited in claim 1 of instant application 10/052,323 filed on 05/18/2009 is an obvious variant of "interrupting or ablating the stratum corneum layer of the epidermis" recited in claims 1 and 93 of co-pending application 10/346,021, despite of slight difference in wordings. Moreover, "a live bacterial vector" recited in the claims of instant application reads on any bacteria that can express endogenous and exogenous nucleic acid in the bacteria; accordingly, a live bacterial vector encompasses any attenuated bacteria by any means, which can be non-replicative as recited in the claims of co-pending application 10/346,021. It is further noted that the specification of co-pending application 11/346,021 states that "Preferably, the vector is a bacterial vector, wherein the bacteria are Escherichia. Preferably, the invention relates to such methods wherein the bacteria are *Escherichia coli*". (See paragraph [0014], claims 2 and 6, US 2004/0009936, publication of 10/346,021) and *E. coli* is encompassed by the limitation "bacterial vector' recited in claim 1 and encompassed by the limitation "gram-negative bacterial vector" recited in claim 45 of instant U.S. application 10/052,323.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In the amendment filed on 05/18/2009, Applicants states that Applicants will consider the above double patenting rejections, including the possibility of filing a terminal disclaimer, upon the determination of allowable subject matter in the present application.

Conclusion

12. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private

PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/
Patent Examiner
Art Unit 1632